OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: [redacted]	Submission Date: June 12, 2007
Brand Name	AndroGel
Generic Name	Testosterone 1% Gel
Reviewer	Manoj Khurana, Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Solvay Pharmaceuticals, Inc.
Submission Type	Supplemental New Drug Application
Formulation; Strength(s)	Testosterone Gel 1%
Indication	Treatment of Constitutional Delay in Growth and Puberty (CDGP) in adolescent males (13-17 years old). **(Under Submission [redacted])** Treatment of hypogonadism in adolescent males (13-17 years old) with a deficiency or absence of endogenous testosterone, regardless of etiology. **(Under Submission [redacted])**

1. Executive Summary

AndroGel® (testosterone gel 1%) has been approved for replacement therapy in adult males (> 18 years) for conditions associated with a deficiency or absence of endogenous testosterone (primary and secondary hypogonadism) (NDA 21-015). The current submission is a pediatric supplemental NDA for AndroGel (testosterone gel) 1% CIII that includes two clinical studies, UMD-01-080 and UMD-01-090. These studies were conducted in order to fulfill a Pediatric Written agreement (Pediatric Written Request). The sponsor proposed two indications, treatment of Constitutional Delay in Growth and Puberty (CDGP) in 13-17 years old adolescent males (NDA) and treatment of hypogonadism in 13-17 years old adolescent males with a deficiency or absence of endogenous testosterone, regardless of etiology (NDA .

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the information provided in the supplement NDA for AndroGel and has found the application not acceptable. This recommendation and the following comment should be sent to the sponsor as appropriate.

The sponsor should address and provide acceptable resolution of the deficiencies identified by the Division of Scientific Investigation's (DSI) audit on the total and free testosterone and dihydrotestosterone (DHT) data from Study UMD-01-080 and Study UMD-01-090.

1.2. PHASE IV COMMITMENTS

None

1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The sponsor has conducted two clinical studies, UMD-01-080 and UMD-01-090.

Study UMD-01-080 was mainly aimed at evaluating the steady-state pharmacokinetics, safety, and tolerability of testosterone in adolescent boys with hypogonadism and CDGP. The following are the key findings of the review of Study UMD-01-080:

- Steady-state pharmacokinetics of total, free and bioavailable testosterone and total DHT was characterized in 17 adolescent boys after once daily application of 0.5 g, 1.5 g and 2.5 g testosterone gel 1% for 4 consecutive days.
- A dose-related increase in exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, $C_{avg,ss}$) was observed for total and free testosterone with increasing doses of testosterone.

Study UMD-01-090 was conducted with an objective of evaluating the clinical response to testosterone gel 1% for the treatment of delayed puberty due to primary or secondary hypogonadism or CDGP, in boys of adolescent age. The following are the key findings of the review of Study UMD-01-090:

- Increases in serum testosterone concentrations were observed in boys diagnosed with delayed puberty due to primary or secondary hypogonadism or CDGP after treatment with testosterone gel 1% starting at a dose of 0.5 g with upward weekly titration.

- The most frequently used final doses were 0.5 g/day, 1.5 g/day, or 2.5 g/day in the hypogonadal population while the most frequently final dose used was 0.5 g/day in the CDGP population.
- The testosterone concentrations achieved in substantial proportion of subjects using the lowest dose of 0.5 g evaluated in the study exceeded the lower bound of the testosterone levels observed in normal adult males (~ 300 ng/dL).
- Two issues with the reliability of systemic exposure data from Study UMD-01-090 were identified. First, approximately half of subjects (41/86) evaluated in this study had less than 80% compliance for dosing. Secondly, ~50% of subjects (n=43) received doses using the [redacted] pump that delivered doses in 0.4 g increments instead of the intended [redacted] pump that should have delivered doses in 0.5 g increment. It appears that this deficiency was identified very late in the trial (May 2005), where the trial was initiated in June 2002.

  Based on the two issues identified above, this reviewer noted three concerns regarding Study UMD-01-090. First, the relationship of observed testosterone exposure increase to the nominal dose increase cannot be relied upon. Second, establishment of 0.5 g dose as the efficacious and safe starting dose is questionable. Third, the sponsor can not claim the following in the label, [redacted]

While this review was being compiled, the DSI completed its audit of the analytical portion of the Study UMD-01-090 conducted at [redacted] The DSI audit identified and reported serious deficiencies with the validation and analytical runs for the assay of total testosterone, free testosterone and DHT (See DSI MEMO Dated 20th NOV 2007). Based on the DSI findings, the assay validity is not acceptable unless the sponsor appropriately addresses the deficiencies. Because the UMD-01-080 study utilized the same assay validation and the same [redacted] laboratory as the UMD-01-090 study, the reliability of data obtained from this study also falls under the same uncertainty.

Therefore, the systemic exposure data of total and free testosterone and DHT from both clinical studies, UMD-01-080 and UMD-01-090, are inconclusive pending an acceptable resolution of the deficiencies identified by DSI and the issues identified with the data resulting from UMD-01-090 study conduct.

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/s/

Sally Choe

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